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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,371	01/16/2007	**Alan Cuthbertson**	PZ0382	3817

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EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
07/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,371	CUTHBERTSON ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *3,7,11,12,14,15,32 and 34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8-10,12,16-31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on April 7th 2009 is acknowledged. Claims 1, 12 and 28 is amended. Claims 3, 11, 13-15, 32 and 34-36 are withdrawn as being drawn to non-elected invention. Claim 7 is withdrawn as being redundant with claim 1. Claims under consideration are claims 1-2, 4-6, 8-10, 12, 16-31 and 33.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/2008 has been entered.

Applicants' arguments, filed 12/16/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Rejection of claims 1-2, 4-6, 8-10, 12, 16-31 and 33.under 35 U.S.C. 103(a) as being unpatentable over Carpenter et al (WO 01/60416) or Mobashery (WO 01/92244) in view of Sahagan (EP 1088550, referenced in the IDS) is maintained for reasons of record restated below.

Amendment of instant claims 1 recited the new limitation "diagnostic imaging in vivo and includes limitation of instant claim7 (currently withdrawn as being redundant).

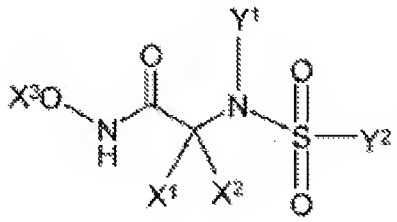
Newly introduced limitation to instant claim 1 "suitable for diagnostic imaging in-vivo" recites the intended use of the instantly claimed compound. Recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed

invention from the prior art. If the prior art structure is capable of performing the intended use, and then it meets the claim. As such the imaging agent derived by an ordinarily skilled artisan from the combination of Carpenter et al and Mobashery who teaches the diagnostic agents of matrix metalloproteinase inhibitors structurally equivalent to that taught by Sahagan who teaches the instantly claimed compounds, would therefore perform the function of the invention as claimed and as such renders the claims obvious.

Limitations of withdrawn instant claim 7, currently incorporated in to instant claim 1 is properly rejected by the rejection below as it was addressed with reference to instant claim 7 in the originally rejection of 07/08/2008.

Original rejection:

The instant claims are drawn towards an imaging agent which comprises a metalloproteinase inhibitor of formula (I) labeled with an imaging moiety which can be detected following administration of said labeled matrix metalloproteinase inhibitor to the mammalian body *in vivo*.



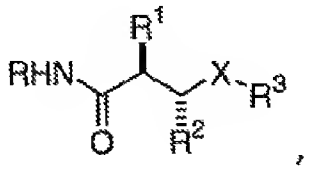
(I)

Further limitations include, the imaging agent wherein the imaging moiety is chosen from a radioactive metal ion, paramagnetic metal ion etc (instant claim 5, 8-13), imaging agent is of formula II (instant claims 6-7), a pharmaceutical composition of the imaging

agent of claim 1 (instant claims 18-21), A conjugate of the MMP of formula (I) with a ligand (claims 22-26) and a kit for the preparation of the radiopharmaceutical composition (claims 27-33).

Carpenter teaches diagnostic agents comprising a diagnostic metal and a compound, wherein the compound comprises: 1:10 targeting moieties; a chelator, and 0-1 linking groups between the targeting moiety and chelator; wherein the targeting moiety is a matrix metalloproteinase (MMP) inhibitor; and wherein the chelator is capable of conjugating to the diagnostic metal (abstract and page 143, claim 1). Carpenter teaches that imaging agents targeted to one or more MMP's would be very useful in detecting and monitoring the degree of extracellular matrix degradation in congestive heart failure, atherosclerosis and other degradative disease processes and these imaging agents, containing a ligand directed at one or more MMP, will localize a diagnostic imaging probe to the site of pathology for the purpose of non-invasive imaging of these diseases (page 5, lines 8-15).

With regard to instant claims 1, 2, 4 and 16-17, Carpenter teaches the details of targeting molecules in his inventions that are MMP inhibitors which are structurally similar to the instantly claimed compounds of formula (I) (page 143-150, claims 4-12 and page 176-188, claims 53-68). For example, one of the compounds claimed in claim 31 is as follows:

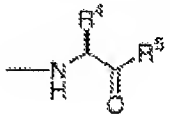


Wherein:

R is independently OH or $-CH_2SH$;

R^1 is independently selected at each occurrence from the group: H, OH, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, and heterocycle-S-CH_2-;

R^2 is independently C_{1-20} alkyl;

X is independently C=O or SO_2, provided when X is C=O, R^3 is  , and when X is SO_2, R^3 is independently selected from the group: aryl substituted with 0-2 R^6, and heterocycle substituted with 0-2 R^6;

R^4 is independently selected at each occurrence from the group: C_{1-6} alkyl, phenyl, and benzyl;

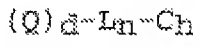
R^5 is independently at each occurrence from the group: NH(C_{1-6} alkyl), NH-phenyl, and NH-heterocycle; wherein said alkyl, phenyl and heterocycle groups are optionally substituted with a bond to L_m;

R^6 is independently aryloxy substituted with 0-3 R^7;

R^7 is independently halogen or methoxy;

With regards to claim 5 Carpenter teaches that the imaging agent may be a MMP inhibitor linked to radioisotope which are known to be useful for imaging by gamma scintigraphy or positron emission tomography (PET) (page 6, lines 15-18) .

With regards to instant claims 6-9 Carpenter teaches a diagnostic agent according having the formula



Where Q is the compound of formula (Ia) or (Ib) which is the matrix metalloproteinase inhibitor; Ln is a linking group and Ch is a metal bonding unit (chelator) which binds to the (pages 163-171, claim 31).

With regards to instant claims 8, 10 Carpenter teaches the diagnostic agent wherein the diagnostic metal is selected from a group consisting of a paramagnetic metal, a ferromagnetic metal, a gamma-emitting radioisotope or an X-ray absorber (page 174, claim 36) and teaches wherein the diagnostic metal is radioisotope selected from the group consisting of ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga and ^{68}Ga. (page 174, claims 37-40).

With regards to instant claims 12, although Carpenter does not explicitly teach the limitations of instant claims 12, Carpenter's teachings of using a radioisotope useful for imaging by gamma scintigraphy or positron emission tomography (page 6, line 15-18) renders this claim obvious.

With regards to instant claims 18-21 Carpenter teaches a diagnostic composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier (page 175, claim 43)

With regards to claims 22-26 Carpenter teaches groups which can be used as linkers between the targeting moieties and the chelator (pages 150-155, claims 13-22)

and the chelator with a metal bonding units (page 155-163, claims 23-30) which can be used in his invention.

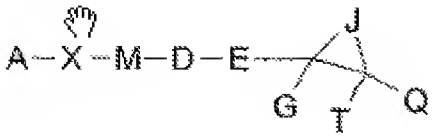
With regards to instant claims 27-33 Carpenter teaches a kit comprising a compound of Claim 1, with one or more ancillary ligands and a reducing agent (page 175, claims 44-47). Although Carpenter does not teach the exclusive limitations of instant claims 27-33, Carpenter teaches the kit comprising of a ligand and a reducing agent and it is obvious to one of ordinary skilled in the art to generate a kit with the components required for generation of the final product.

With regards to instant claims 34-36 Carpenter teaches a method of detecting, imaging or monitoring atherosclerosis in a patient by administering a diagnostic agent of claim 1 and acquiring an image of the site of concentration of said diagnostic agent (page 204, claims 95-98).

Accordingly, Carpenter provides one of ordinary skill in the art motivation to prepare an imaging agent by synthesizing compounds structurally similar to those taught by carpenter, attach an imaging moiety to the compound with or without a linker, prepare compositions and kits of the imaging agent and use it in the diagnosis of cardiovascular diseases especially atherosclerosis.

Mobashery also teaches compounds that inhibit matrix metalloproteinase in *vivo* and in *vitro;* and a method for imaging a tumor *vivo* or *vitro* (abstract).

With regards to instant claims 1,2, 4, 16 and 17 Mobashery teaches compounds of formula (I)



(I)

wherein

A-X-M is a hydrophobic group;

D is O, S, (C_1-C_6)alkyl, a direct bond, SO_2, SO, C(=O)NR, C(=O)O, NRC(=O), or OC(=O);

E is a direct bond, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl, wherein any alkyl, cycloalkyl, alkenyl, or alkynyl of E is optionally substituted with one or more (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, cyano, nitro, halo, SR, NRR, or COOR, wherein each R is independently H or (C_1-C_6)alkyl;

J is S or O;

G, T, and Q are each independently H, (C_1-C_6)alkyl, or cyano;

or a pharmaceutically acceptable salt thereof.

which are structurally related to the instantly claimed compounds (pages 44-45, claims 1-4).

With regards to instant claims 5, 8, 10 and 12 Mobashery teaches that the radiolabeled compounds of formula (I) are also useful as imaging agents for imaging cells comprising MMP's. Accordingly, the invention also provides compounds of formula (I) that include one or more detectable radionuclides which can be incorporated into the compound by replacing an atom of the compound of formula(I) with a radionuclide (e.g. nonmetallic radionuclide) or the radiolabeled compound can be prepared by linking a compound of formula (I) to a chelating group that includes a detectable radionuclide which renders these claims obvious (page 20, lines 8-19; pages 48-48, claims 25-30).

Mobashery teaches the "detectable radionuclide" as any suitable radionuclide useful in a diagnostic procedure in vivo or in vitro and suitable detectable radionuclides include metallic radionuclides and non-metallic radionuclides (page 21, lines 3-7) Mobashery additionally teaches that the non-metallic radionuclide can be a non-metallic paramagnetic atom (e.g., Fluorine-19); or a non-metallic positron emitting radionuclide (e.g., Carbon-11, Iodine-123) (page 20, lines 31-33) (page 49-50, claims 25-30)

With regards to instant claims 6-9 Mobashery teaches that the “chelating group” is a group that includes a detectable radionuclide and any suitable chelating group can be employed. In addition Mobashery provides several references which disclose suitable chelating groups (page 20, lines 19—page 21, line 2).

With regards to instant claims 18-21 Mobashery teaches the pharmaceutical compositions of the compounds of formula (I) that comprises a radiolabeled compound of formula (I) and a pharmaceutically acceptable carrier (page 5, lines 25-27 and page 26, lines 6-13, page 49, claim 24 and page 50, claim 31).

With regards to instant claims 22-26 Mobashery teaches a combination of the compound of his invention with a chelating group comprising a detectable radionuclide (page 50, claim 28).

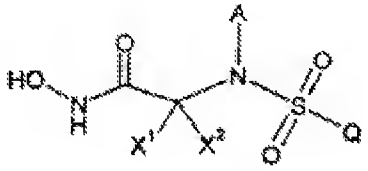
With regards to instant claims 34-36 Mobashery also provides a compound of formula (I) that comprises a radionuclide, or a pharmaceutically acceptable salt thereof for use in medical diagnosis which includes processes involving modulation of MMP activity such as angiogenesis, inflammation, cardiovascular diseases etc. (page 6, lines 5-10).

Accordingly Mobashery provides one of ordinary skills in the art motivation to develop matrix metalloproteinase inhibitors conjugated to a detectable moiety for use in diagnosis of diseases associated with MMP activity.

What both Carpenter and Mobashery do not teach is the radio labeling of the specific matrix metalloproteinase inhibitors of the formula recited in the instant claims.

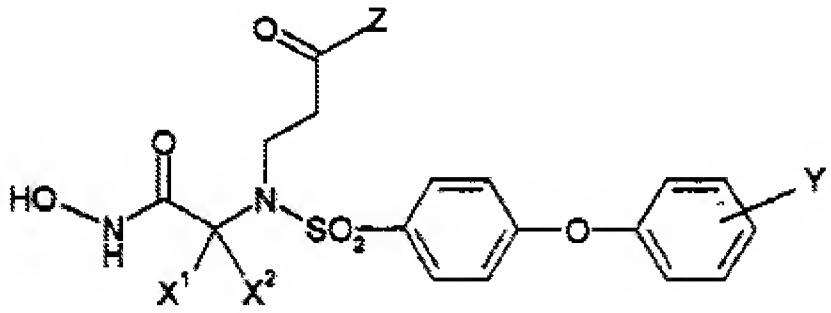
This deficiency is cured by the teachings of Sahagan et al.

Sahagan teaches methods of using a compound of formula (I) (abstract, claim 1.



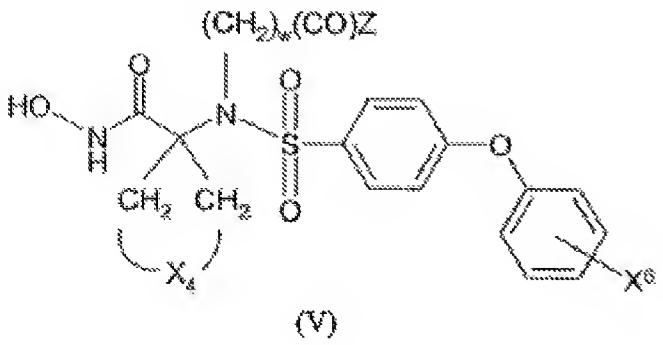
(I)

Substituents for the variables in the formula (I) above as taught by Sahagan reads on the matrix metalloproteinase inhibitors claimed in the instant applications. Sahagan teaches that one preferred methods of the invention comprise the administration of the formula (Ic) below (lines 1-10, page 5):



(Ic)

this is structurally similar to the instantly claimed compound (V)



(V)

Sahagan teaches that the compounds of his invention are inhibitors of zinc matrix metalloendopeptidases especially those belonging to the matrix metalloproteinase (MMP) (page 2, paragraph [0002]) and can be used to treat several diseases which are characterized by metalloproteinase activity (page 10, paragraph [0045]). Accordingly, Sahagan is drawn to the same class of compounds disclosed in Carpenter and Mobashery.

Sahagan teaches that the method of treatment as per his invention also includes isotopically-labeled compounds, which are identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different form the atomic mass or mass number usually found in nature. Additionally, Sahagan teaches that the compounds relating to the present invention, prodrugs thereof , and pharmaceutically acceptable salts of said compounds or of said prodrugs which contains the isotopes are within the scope of his invention (page 10, paragraph [0043]).

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. It would have been *prima facie* obvious to the skilled artisan to develop diagnostic imaging agents comprising a matrix metalloproteinase inhibitors taught by Sahagan conjugated to an imaging moiety as taught by Carpenter or Mobashery. An ordinarily skilled artisan would have been motivated to use matrix metalloproteinase inhibitors compound taught in the prior art and conjugate it to a radioactive imaging moiety through a linker or a chelator for use in diagnosis of cardiovascular diseases since the prior art as taught by Carpenter and Mobashery have already shown that these compounds can be successfully used for diagnostic purposes when conjugated to an imaging moiety. Furthermore, using the imaging agents to develop a pharmaceutical composition or kit would have been obvious to one of ordinary skill in the art at the time of invention since the prior art teaches compositions and kits developed using similar compounds.

A skilled artisan will be able to develop such a dosage form with a reasonable expectation of success based on the state of the art at the time of invention in order to provide imaging agents comprising a matrix metalloproteinase inhibitors conjugated to an imaging moiety for diagnosis of cardiovascular diseases, since the imaging of MMP's in the heart would be useful for the localization and monitoring the progression/regression of a variety of cardiac diseases which are associated with alterations in the MMP content of the cardiac tissues.

Response to applicant's arguments filed on 04/07/2009:

Applicant traverses the above rejection with the following arguments:

a. Carpenter provides no in-vivo imaging data to demonstrate the efficacy for any of the in vivo imaging applications and in the absence of such data the person skilled in the art would not be motivated to build on the teaching of Carpenter/Sahagan. There are significant differences between Carpenter and Sahagan references in terms of the structures taught, which makes logical combination of Carpenter/Sahagan actually teach away from the present invention.

b. Sahagan refers to medicaments for the treatment of a mammal, together with related prodrugs and the radioisotopes used by Sahagan is intrinsic to the molecule and 3H and 14C are not suitable for medical imaging. Applicants content that the chelator labeling methodology of Carpenter cannot be applied to Sahagan since Sahagan, teaches replacing "one or more atoms by an equivalent radioisotope" which contradicts the approach taken by Carpenter, where radio-metal complexes are attached. Applicant argues that the amendment of instant claim 1 to include “in-vivo imaging” clarifies that the instant invention is towards medical imaging and the ^{14}C used in the breath test as stated by the examiner in the office action dated 01/07/2009 is not for imaging purposes.

c. There is no structural similarity between Mobashery's compounds and the instantly claimed compounds and teaching so Sahagan on which radiolabels are suitable would preclude the attachment of radio metals as chelator metal complexes. Mobashery does not synthesize or test any radio-labeled compound and does not provide any showing of proof of concept for imaging.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

With respect to arguments by the applicants about Carpenter not teaching any in –vivo data, Carpenter in combination with Mobashery and Sahagan provides ample suggestion to an ordinarily skilled artisan to develop an imaging agent as instantly claimed. The in-vivo limitation of the instant claim is an intended use of the instantly claimed imaging agent. Recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, and then it meets the claim. As such the imaging agent derived by an ordinarily skilled artisan from the combination of Carpenter et al and Mobashery who teaches the diagnostic agents of matrix metalloproteinase inhibitors structurally equivalent to that taught by Sahagan who teaches the instantly claimed compounds, would therefore perform the function of the invention as claimed and as such renders the claims obvious. Additionally, Mobashery provides in-vitro testing data for his compounds which are functionally equivalent to compounds of Carpenter and as such an ordinarily skilled artisan would have a reasonable expectation of the compounds being used as diagnostic agent based on the combined teachings of Carpenter and Mobashery. With respect to applicant's argument

regarding the structural similarity between the compounds taught by Carpenter and the instant application, Examiner finds the applicant's argument partially persuasive. While agreeing with the Applicant's that the compounds of Carpenter are not structurally identical to the instantly claimed compounds, Examiner would like to point out they are functionally equivalent since they are both matrix metalloproteinase inhibitors and posses a similar skeletal structure. Carpenter also explicitly teaches a diagnostic agent comprising a diagnostic metal and a compound where in the compound comprises a matrix metalloproteinase inhibitor and a chelator which reads on the instantly claimed imaging agent. In combination with Sahagan who teaches the instantly claimed compound as matrix metalloproteinase inhibitors an ordinarily skilled artisan would be motivated utilize the compound taught by Sahagan in the diagnostic imaging agent taught by Carpenter thus arriving at the instantly taught imaging agent.

With reference to applicant's arguments against Sahagan, Sahagan teaches the instantly claimed compounds also include isotopically-labeled compounds. Examiner would like to point out that ^{14}C can be used for imaging purposes, for example ^{14}C labeled antiviral drug is used a as probe for selectively imaging brain infection in a rat model of quantitative Autoradiography,

With reference to applicant's arguments against Mobashery, Examiner would like to point out that Mobashery also teaches matrix metalloproteinase inhibitors and a method of imaging a tumor *in-vivo* and *in-vitro*. Mobashery teaches matrix metalloproteinase inhibitors which are functionally equivalent to the compounds of both Carpenter and Sahagan. Mobashery additionally teaches radiolabeling such

compounds either by incorporating the radiolabel in the compound or by linking the compound to a chelating group that includes detectable radionuclide. In combination with Sahagan who teaches the instantly claimed compound as matrix metalloproteinase inhibitors an ordinarily skilled artisan would be motivated to utilize the compound taught by Sahagan in the diagnostic imaging agent taught by Mobashery thus arriving at the instantly taught imaging agent. Incorporation of radionuclide into a compound either through incorporation or through linking a chelating agent was well known in the art at the time of the invention and as such it would be obvious to an ordinarily skilled artisan utilize the compounds taught by Sahagan (which includes the instantly claimed compound) and radiolabel the compound appropriately for its use as diagnostic agent.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As such, Examiner on page 18 of the office action dated 07/08/2008, explicitly states that Carpenter and Mobashery do not teach the radio-labeling of the specific matrix metalloproteinase inhibitors of the formulas recited in the instant claims. It is the teachings of Carpenter or Mobashery when taken in combination with Sahagan which renders the instant claims obvious.

It is noted that , "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v.

Teleflex, 127 S,Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." Id. at 1742. Consistent with this reasoning, it would have obvious to for a person of ordinary skill to utilize the teachings of Carpenter and Sahagan and combine them to arrive at the instantly claimed imaging agents.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Carpenter and Mobashery explicitly teach diagnostic agents of matrix metalloproteinase inhibitors in combination with a chelator through a linker for diagnosis or treatment of cardiovascular conditions. Sahagan teaches instantly claimed compounds as matrix metalloproteinase

inhibitors which can be radio-labeled. Accordingly an ordinarily skilled artisan will be motivated to combine the teachings of Carpenter and Mobashery with that of Sahagan to arrive at the instantly claimed imaging agent with a reasonable expectation of success based on the state of the art at the time of invention in order to provide imaging agents comprising a matrix metalloproteinase inhibitors conjugated to an imaging moiety for diagnosis of cardiovascular diseases, since the imaging of MMP's in the heart would be useful for the localization and monitoring the progression/regression of a variety of cardiac diseases which are associated with alterations in the MMP content of the cardiac tissues. In It is also noted that "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including non-preferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

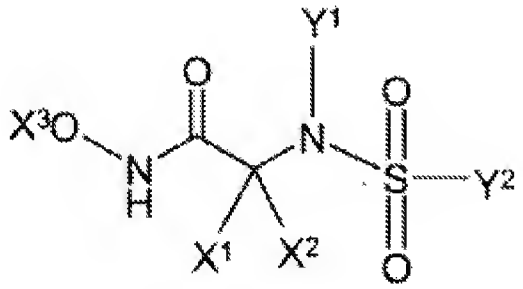
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by,

or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

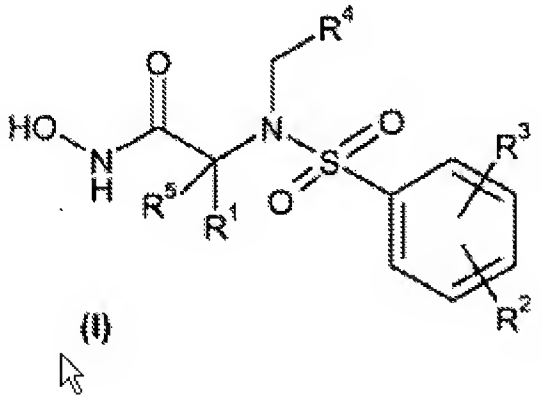
Claims 1-2, 4-10, 13 and 16-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-21, 24-28, 30-31, 35 of copending Application No. 10544945 (copending '945). Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 1 is generic to the compound that is recited in claim 1 of copending '945. That is, claim 1 if copending '945 falls entirely within the scope of claim 1 or, in other words, instant claim 1 is anticipated by claim 1of copending '945. Specifically, the compound of claim 1 of the copending '945 is the compound of instant claim 1 where in the formula $[A^1]_p[O]_qA^2$ for Y^2 p=0 and q=0 and A2 is C_{6-10} aryl. Instant claims compare to the copending '945 as follows:

1. Claims 1-4, 6 and 14-17 of instant application are drawn to an imaging agent which comprises a metalloproteinase inhibitor of general Formula (I) (shown below) labeled with an imaging moiety.



(I)

Claim 1-4 of co-pending '945 recites a diagnostic imaging agent which comprises a matrix metalloproteinase inhibitor of formula **I** (shown below) labeled with a γ-emitting radionuclide.



(I)

The specific compound claimed in the composition of claims 1-18 of copending '945 is a specie of the genus of compounds claimed in the composition of instant claims 1-2, 4-10, 13, 16-19 and 22-26.

2. In the instant application claims 5, 7 and 10 recites the specifics of the imaging moiety of the imaging agent claimed in instant claim 1. Claims 5, 7-9, 10-14 of copending '945 recites similar limitations with reference to the imaging moiety of the diagnostic imaging agent claimed in copending '945 claim 1.

3. Claims 8-9, 22-26 of the instant application recites the limitations with reference to the ligand and the conjugate of imaging agent claimed in instant claim1. Claims 15-18 of copending '945 recites similar limitations with reference to the ligand and the conjugate of diagnostic imaging agent claimed in copending '945 claim 1.

4. Claims 18-21 of the instant application are drawn towards pharmaceutical or radiopharmaceutical compositions which comprises the imaging agent of instant claim 1. Claims 19-21 of copending '945 are drawn towards a pharmaceutical composition comprising the diagnostic imaging agent of copending '945 claim 1.

5. Claims 27, 29-31 of the instant application are drawn to a kit for the preparation of the radiopharmaceutical composition of instant claims 20-21. Claims 24-28 and 35 of copending '945 are drawn to a kit for the preparation of the pharmaceutical composition of copending claims 19-20.

Therefore subject matter disclosed in claims 1-2, 4-10, 13 and 16-31 of the instant application is fully taught in claims 1-21, 24-28 and 35 of copending '945 and are hereby rejected under the judicially created doctrine of obviousness-type double patenting.

Conclusion

Claims 1-2, 4-10, 13, 16-31 and 33 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

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